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YEAR IN CARDIOLOGY SERIES

The Year in Echocardiography

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The year in echocardiography has been marked by incremental progress in our understanding of the methodology and potential applications of techniques introduced in the last few years, such as speckle tracking (STE), real-time 3-dimensional echocardiography (RT3DE), and Doppler tissue imaging (DTI). Much of our understanding of these techniques came through comparisons with independent methods and attempts at their application to complex problems, such as the measurement of left ventricular torsion and untwisting velocity in the assessment of diastolic function and the characterization of dyssynchrony and response to cardiac resynchronization therapy in patients with advanced heart failure. Myocardial contrast echocardiography (MCE) also has provided new insights in the physiology of the coronary circulation, and the role of myocardial contrast echocardiography in the clinical assessment of coronary perfusion defects continues to evolve. Progress also was made in understanding the strength of the relationship between patent foramen ovale (PFO) and stroke and in understanding the operative risk and response to surgery in patients with low-flow, low-gradient aortic stenosis. Although a discussion of every topic in echocardiography is beyond the scope of this review, an attempt is made to highlight and discuss those areas that are novel and in which progress has been the greatest.

Torsion

Background. One of the ongoing challenges in echocardiography has been the development of an accurate method for assessing left ventricular diastolic function that does not require pressure measurement and is "relatively" load independent. Current echo-Doppler methods for assessing left ventricular (LV) diastolic function depend on measurements of 1) the time-varying velocity of blood flow into the ventricle, 2) the rate of change in LV volume, or 3) the extent and velocity of myocardial motion (i.e., E′). Because all of these measures are dependent on the volume of blood entering the ventricle, they do not begin until after the opening of the mitral valve, which occurs after the majority of LV relaxation has been completed and relate to both LV and left atrial pressures. Importantly, these measures provide little information about the isovolumic relaxation period (beyond its duration) when the majority of relaxation occurs (1).

One approach for noninvasively assessing isovolumic relaxation is through the measurement of the degree of LV twisting (torsion) that occurs during systole and the rate of untwisting during diastole. Torsion occurs in the normal heart because the orientation of the myocardial fibers varies across the wall. The subendocardial fibers have an approximately longitudinal orientation with and angle of ~80° relative to the circumferential plane. This angle decreases toward the mid-wall, where the fibers are circumferentially oriented (0°), and decreases further to an oblique orientation of approximately −60° at the subepicardium (2). When these obliquely spiraling subepicardial and subendocardial fibers contract, they produce a twisting or wringing motion (torsion) of the LV. Because the vectors of contraction occur at roughly equal angles (but with opposite signs) relative to the ventricular long axis, the 2 contractile moments tend to counterbalance each other. However, because of the larger radii and therefore greater torque of the subepicardial fibers, they predominate. When viewed from the apex, systolic contraction of the ventricle is characterized by the counterclockwise rotation of the apex and clockwise rotation of the base, resulting in a twisting or wringing motion. Because the degree of torsion is a function of the contraction of the LV, the amount of torsion in degrees varies linearly with ejection fraction and stroke volume. Diastolic recoil or "untwisting" is related to the systolic compression of elastic proteins and is largely (~40%) an isovolumic event and thus volume independent. The rate of untwisting, or the relaxation rate, has been shown to correlate reasonably well with the relaxation time constant τ and to be independent of left atrial pressure (1). At a functional level, elastic recoil contributes to the development of the intracavitary gradient that precedes mitral valve opening (diastolic suction [3][1]) and must be present before filling can begin (4,5). The relaxation rate also has been shown to remain constant during volume loading and to be more closely related to τ

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[1]Note that suction is classically used to describe the ability of a ventricle that has contracted to below its equilibrium volume (the volume at 0 pressure) to generate negative pressures when relaxing at a fixed volume. However, in the echo-Doppler context the term "suction" is frequently used to refer to the way the intraventricular pressure gradient promotes the movement of blood to the apex, allowing efficient filling at low left atrial pressures.

than the isovolumic relaxation time. As a result, it has been suggested that the rate of recoil or untwisting might be a more direct and therefore superior measure of diastolic function than conventional echo Doppler measures of filling related parameters (1).

Novel echocardiographic approaches. Two echocardiographic methods have been proposed to measure torsion: DTI and STE, both of which have been shown to correlate with magnetic resonance imaging (MRI) when used in small groups of patients (6,7). Building on these feasibility data, more recent studies have sought to further define the hemodynamic correlates of torsion in normal patients as well as the effects of age, gender, and exercise on measure of torsion and untwisting rate.

Echocardiographic findings in normal patients. EFFECTS OF AGE. Because cardiac cellular structure and function change from infancy to adulthood, it is reasonable to ask whether torsional biomechanics also change. In a study of 45 normal subjects ranging in age from 9 days to 49 years, Notomi et al. (8) observed by using DTI that LV torsion increased with age, owing primarily to the augmentation of basal clockwise rotation during childhood and apical counterclockwise rotation during adulthood (torsion = 5.8 ± 1.3°, 6.8 ± 2.3°, 8.8 ± 2.6°, 8.7 ± 2.7°, and 13.8 ± 3.3° for infants, children, adolescents, young adults, and middle-aged adults, respectively). Although peak LV torsion and untwisting velocity showed age-related increases, when normalized by LV length, greater values were observed in infants and middle-aged patients. The proportion of untwisting during isovolumic relaxation was lowest during infancy and increased progressively being highest in middle age; however, peak normalized untwisting velocity (peak untwisting velocity normalized by peak LV torsion) showed a decrease in adulthood (8). In another study of 118 adults, Takeuchi et al. (9), using STE, similarly examined the effects of aging on torsion and untwisting. Patients were divided in 3 groups (young, <40 year [n = 57]; middle-aged, 40 to 60 years [n = 41]; and older subjects, >60 years [n = 15]). Torsion increased with age being 6.7 ± 2.9°, 8.0 ± 3.0°, and 10.8 ± 4.9° in young middle age and older subjects, respectively. Untwisting rates were significantly lower in middle age (0.40 ± 0.22%/ms) and older groups (0.41 ± 19%/ms) than in the young group (0.64 ± 0.42%/ms) No gender differences were noted in peak twist or untwisting velocities (9).

EFFECTS OF EXERCISE. In a study of 20 normal volunteers, Notomi et al. (3) using DTI measured the LV rotational velocities at the base and apex of the LV and from their difference calculated the magnitude and velocity of twist and untwisting throughout the cardiac cycle. They reported that submaximal exercise increased LV torsion from 11 ± 4° to 24 ± 8°, which was associated with an increase in LV diastolic and decrease in LV systolic volume. Left ventricular untwisting began just before aortic valve closure at rest and during exercise. Peak untwisting velocity (rest = −2.0 ± 0.7 radians/s vs. exercise −5.6 ± 2.3 radians/s) occurred slightly after mitral valve opening at rest, with the separation increasing during exercise. In both cases, peak-untwisting velocity preceded the peak intraventricular pressure gradient that was followed by the peak E wave velocity. In each case, the peak intraventricular pressure gradient occurred at the inflexion point of the torsion-volume curve. This pattern was in contrast to the peak long-axis lengthening and short-axis expansion velocities that occurred virtually synchronously with peak E velocity, suggesting that they were a consequence rather than a cause of transmitral filling. In normal patients, ~40% of untwisting occurred during isovolumic relaxation, with an additional 40% occurring by the time of peak early filling, reflecting the time during which intraventricular pressure gradients develop. Although the peak untwisting velocity correlated modestly with the magnitude of the peak intraventricular pressure gradient at rest (r = 0.41, y = 0.31, x = 0.77) this relationship decreased to r = 0.36 with a slope of 0.19 with exercise. Although the correlation improved to r = 0.75 when the 2 groups were combined, the subgroup r^2 =~0.16 suggests that factors in addition to the peak untwisting velocity are important to the intraventricular pressure gradient. The authors also examined a small group of subjects with hypertrophic cardiomyopathy and observed that although peak torsion was greater at rest compared with normal patients, it was not significantly augmented with exercise and untwisting was delayed and was almost coincident with the peak of early filling. In another study of world-class athletes, Neilan et al. (10) showed that torsion increased from 10 ± 4° at baseline to 15 ± 5° at the end of a 2,000-m world indoor rowing championship. The smaller increase in torsion after much more strenuous efforts may reflect the difference in measurements made during versus after exercise.

In a validation study comparing STE to sonomicrometer measurements, Helle-Valle et al. (11) found an excellent correlation between the 2 methods for apical rotation (r = 0.98, y = 0.98x − 0.39); however, for basal rotation, the correlation decreased slightly (r = 0.76, y = 0.58x − 1.20). Conversely, the correlation of the time to peak rotation was better at the base (r = 0.9) than at the apex (r = 0.58). Both methods showed corresponding increases in rotation during dobutamine infusion and decreases in apical rotation after left anterior descending artery (LAD) ligation without affecting basal rotation (11). In the clinical portion of the study, the authors compared STE with MRI tagging and also found good overall correlations; however, again, the correlation for peak apical rotation was better than that for basal rotation (r = 0.91 vs. r = 0.67)

Perspective. Although torsion is a conceptually simple measure, in practice it appears more complex. Consideration of the variation in torsion measurements in the studies cited previously (Table 1) suggests some of these issues (3,8–11). In these 5 studies of presumably normal subjects of roughly comparable ages, there was wide variability in the reported values for resting systolic torsion. There are many potential

Table 1 Reported Values for Torsion in Normals of Similar Age

Author	Method	Subjects (n)	Age (yrs)	Torsion
Takeuchi et al. (9)	Speckle tracking	57	29 ± 6	6.7 ± 2.9°
Notomi et al. (8)	DTI	10	28 ± 3	8.7 ± 2.7°
Neilan et al. (10)	Speckle tracking	17	37 ± 9	10 ± 4°
Notomi et al. (3)	DTI	20	34 ± 7	11 ± 4°
Halle-Valle et al. (11)	Speckle tracking	29	33 ± 6	14.5 ± 3.2°

DTI = Doppler tissue imaging.

reasons for these differences. First, torsion varies regionally around the ventricle, increases from epicardium to endocardium, and is nonlinear from apex to base (12). Because the greatest amount of twist occurs at the apex, the position of apical sampling would appear to be critical and is difficult to precisely standardize. Second, STE is dependent on the quality of the 2-dimensional images, and subendocardial speckles have been noted to be more easily identified than subepicardial echoes. Preferential subendocardial sampling, however, may increase torsion values because subendocardial torsion is nearly twice that of the subepicardium (11,13).

Furthermore, during relaxation, the subepicardial fibers relax before the subendocardial fibers and, hence, sampling location may affect timing measures. Third, STE at the base may be complicated by through plane translation that may explain the poorer correlations for basal rotation when compared with reference standards. Fourth, correction is often necessary for ventricular size because when torque is applied to a cylinder, the angle of twist it produces and the associated shear stress are proportional to the magnitude of the torque and the shaft length (ventricular length). Thus, although absolute torsion in infants was less than in adults, LV_{tor} normalized for ventricular length was greater in infants than in older children, adolescents, and adults, which is consistent with the higher contractility noted in infants (8). Likewise, the mouse heart has an apex to base angular deformity that is a fraction of the human value; however, when normalized for LV length, the 2 species become equal (14). Fifth, peak rotation of the apex and base do not necessarily occur at the same time, with the result that instantaneous peak torsion may be smaller than the difference between peak apical and peak basal rotation. Finally, torsion varies with changes in preload, afterload, and contractility. In the experimental model, torsion was shown to increase with increasing end-diastolic volume at constant end-systolic volumes and to decrease with increasing end-systolic volumes at constant end-diastolic volumes. In volume-loading studies, both end-diastolic and end-systolic volumes tend to increases in parallel and the relative forces therefore tend to balance each other. Inotrophic stimulation increases torsion, as does increasing afterload. Left ventricular hypertrophy has been shown to increase torsion, presumably as the result of an increase in the radius of the subepicardial fibers relative to the subendocardial fibers, although subendocardial ischemia also may contribute (15–17).

Thus, although MRI studies have already provided a great deal of mechanistic information about torsion, the use of this information clinically has been limited. It is hoped that because of its wider availability and better temporal resolution, Doppler echocardiography can extend this understanding to clinical practice and may provide unique insights into our understanding of "diastolic function"; however, there are still technical issues that need to be better understood.

3-Dimensional Echocardiography

Comparison with cardiac computed tomography (CCT). Studies to validate the accuracy and define differences between real-time 3-dimensional echocardiography (RT3DE) and other currently available methods for calculating LV volume and ejection fraction continue. The use of RT3DE and CCT measures of cardiac size and function were compared with a standard reference technique, cardiac magnetic resonance imaging (CMR) in 31 patients. Left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes and ejection fraction (EF) were computed for each technique from radial long-axis images. Both CCT and RT3DE measurements of LVEDV, LVESV, and EF correlated closely with CMR (r^2 = 0.93 to 0.96) with a slightly lower correlation for the CCT EF (r^2 = 0.85). Although CCT provided highly reproducible measurement of LV volumes, they were significantly larger than CMR values (mean 26 and 19 ml, respectively), whereas the EF was slightly but significantly underestimated (−2.8%). In contrast, mean RT3DE values slightly but not significantly underestimated CMR EDV and ESV (−5 and −6 ml, respectively) with no bias in EF measurement. The use of RT3DE showed greater interobserver variability than CCT (EDV = 11.2 ± 8.6% vs. 2.6 ± 2.0%, ESV = 14.2 ± 11.85% vs. 7 ±5.2%, and EF = 10.5 ± 8.3 vs. 6.5 ± 4.9, respectively) with CMR in general showing intermediate values. Image analysis time for each dataset including retrieval was ~20 to 40 min. This study points out the differences in these 3 three-dimensional imaging techniques that may be of importance in clinical settings, such as the selection of patients for and evaluation of response to cardiac resynchronization therapy (CRT) therapy (18).

To assess the accuracy of RT3DE in more complex ventricles, Chan et al. (19) compared LVEDV and LVESV determined by both MRI and RT3DE in 30 patients with prior myocardial infarction (MI) and regional wall motion abnormalities. There was an excellent correlation between RT3DE and MRI for both LVEDV ($r^2 = 0.81$) and LVESV ($r^2 = 0.88$), with RT3DE slightly underestimating MRI (EDV, mean difference = 10 ± 26 ml; ESV mean difference = −0.9 ± 19) (19). In a similar RT3DE/MRI comparison of 26 younger patients with congenital heart disease, van den Bosch et al. (20) reported correlations of r = 0.97 for EDV, r = 0.98 for ESV, and r = 0.94 for EF. Calculation of the same values using an automated border-tracking algorithm proved less reliable (20).

In other studies comparing RT3DE with MRI in small groups of patients, it was shown that: 1) contrast, not surprisingly, improved wall motion analysis in patients with poor RT3DE image quality (21) as well as during exercise when compared with MRI (22); 2) RT3DE could accurately determine, with good image quality, LV mass in patients with congenital heart disease (23); 3) the normal tricuspid annulus has a bimodal shape with distinct high points located anteriorly and posteriorly and becomes larger, more planar, and more circular in patients with moderate or severe tricuspid regurgitation (24); and 4) RT3DE could accurately measure the size of a ventricular septal defect in comparison with surgical measurement (25).

Myocardial Contrast Echocardiography

Comparison with single-photon emission computed tomography (SPECT) imaging for the detection of coronary artery disease (CAD). In a prospective multicenter study MCE was compared with SPECT (a semiquantitative comparison) for the detection of coronary artery disease in 123 patients with symptoms suggestive of CAD. Intermediate (mechanical index 0.5) triggered-replenishment MCE using a lipid-stabilized suspension of perfluorobutane microbubbles (Sonazoid, Nycomed-Amersham Imaging, Oslo, Norway) was performed concurrent with vasodilator stress SPECT. Coronary angiography performed within 4 weeks revealed CAD (≥50% stenosis) in 78% of patients with 90% having ≥70% stenosis. In this population, with a high pretest probability of disease, there was no difference in the sensitivities of MCE and SPECT in the detection of CAD (84% vs. 82%) and both had similar specificities (56% vs. 52%), respectively. In patients with multivessel disease, the sensitivities of MCE and SPECT also were similar (91% vs. 88%, respectively). However, when patients with prior MI and resting perfusion defects were excluded, the sensitivities of MCE and SPECT were 75% and 67% with specificity of 62% and 65%, respectively (26). There was no mention of patients excluded for image quality or segments/regions that could not be visualized, which is unusual for an MCE study. This study is consistent with several other recent studies that report similar sensitivities for MCE and SPECT. The authors contrast their results to a previous multicenter study by Marwick et al. (27) that reported lower sensitivities and attribute their improved results to improved technology and expertise. Although advances have clearly occurred, the earlier study also was intended to simulate the results obtained when MCE was applied in routine practice as opposed to data from academic/university programs and in unselected patients this remains a problem.

Quantitation of regional perfusion. Because the visual interpretation of MCE studies is inherently subjective and because differences in image intensity should be quantifiable, Malm et al. (28) attempted quantitative MCE imaging during low-power pulse inversion adenosine vasodilator stress in 53 consecutive patients referred for coronary angiography because of suggested CAD. Ten patients initially were excluded because of poor image quality, whereas another 7 had to be excluded because of imaging difficulties during stress and, in an additional 3, the MCE protocol was aborted because of atrial fibrillation (n = 2) or chest pain (n = 1). Thus, a complete dataset could be obtained for analysis in only 35 of 55 patients (64%). Of the 99 coronary territories available for comparison with MCE, 55 were normal or had no significant stenosis, whereas 44 were supplied by stenosed vessels. At rest, there were no significant differences between groups in A (peak contrast intensity reflecting myocardial blood volume), β, (rate of increase in contrast intensity after a destructive pulse reflecting the mean blood flow velocity) and $A \times \beta$ (representing myocardial blood flow). During hyperemic stress, A did not differ between groups but β, and $A \times \beta$ were significantly lower in the group with significant stenosis. Sensitivity and specificity were better for LAD stenosis than for stenosis in left circumflex artery, right coronary artery, or multivessel disease, including LAD stenosis (accuracy 89%, 65%, 69%, and 73%, respectively). Of note in patients with ≥75% stenosis, even resting values of A, β, and $A \times \beta$ tended to be lower than in territories without significant stenosis. The authors conclude that although myocardial blood flow and myocardial blood flow velocity reserves can accurately identify significant coronary disease in selected patients, this technique is limited by imaging artifacts and time-consuming analysis, and the diagnostic accuracy seems sufficient only for LAD stenosis (28).

Microcirculatory function. The use of MCE has proven particularly valuable in advancing our understanding of the microcirculation. For example, coronary stenoses are known decrease microvascular blood flow reserve not only in the stenotic territory but also in adjacent territories supplied by nonstenotic arteries. Although it has been postulated that communication between adjacent territories through collateral vessels underlies the flow reserve abnormalities, the exact mechanism is unknown. In an experimental study, epicardial flow (flow probe), total flow (epicardial and collateral contributions), flow through the microcirculation (vessels <10 μm [i.e., microspheres]), and regional myocardial blood volume (MCE) were measured separately to isolate the individual contributions to each flow territory. At baseline, an LAD stenosis increased LCx epicardial flow without changing myocardial flow, as measured by microspheres indicating epicardial collateral flow from the LCx to LAD beds. During adenosine infusion, LCx flow reserve was significantly less during noncritical LAD stenosis than without stenosis (4.7 ± 1.6 vs. 2.8 ± 1.1). This result was associated with an increase in MCE-derived blood volume at end-systole (reflective of blood volume in the microcirculation [vessels <200 μm]). There was also a strong trend toward a negative linear relationship (r = −0.67) between stenosis severity (gradient across the stenosis) and the magnitude of flow reserve reduction. This increase in blood volume was felt to reflect compensatory recruitment of microvascular collateral networks between 10 and 200 μm (detected by MCE for their contribution to blood volume but not by microspheres because they pass through vessels of this size into the stenotic bed) that augment stenotic bed flow reserve but at the expense of the adjacent bed (29).

Bioeffects of contrast agents. Previous studies in small animal models have suggested that destruction of microbubbles can produce adverse effects, including ventricular ectopy, increased vascular permeability, and even cell death in exposed tissues. In a study designed to more closely simulate the clinical situation, the effects of contrast destruction were examined using Evans Blue dye (a marker of vascular permeability) and propidium iodide staining (a marker of cell death) to assess the effects of MCE in both an open and closed chest canine model. The MCE studies were performed using a commercially available agent (Definity, Bristol-Myers-Squibb Billerica, Massachusetts) and a clinical ultrasound machine (Vingmed System V, General Electric, Cincinnati, Ohio) operating at available clinical power settings (mechanical index 1.0 and 1.8) and frequency (1.5 MHz). In the open chest model, intermittent (single-frame triggering at end-systole every fourth beat for 10 min) short-axis scanning produced a full-thickness blue band (10- to 15-mm wide) in the anterior wall along the path of the scan plane at a mechanical index of 1.8 that also was present but less pronounced after scanning at mechanical index 1.0. The content of Evans blue significantly increased at both power levels, but the concentration at mechanical index 1.8 was roughly 3 times that at mechanical index 1.0, and petechiae, along with increased counts of propidium iodide, were noted only at the higher mechanical index. In the closed chest model, intermittent scanning (dual frame at end-systole for 10 min) in a modified 4-chamber view at an estimated mechanical index of ~1.6 (after correction for attenuation) resulted in increased Evans blue staining. Propidium iodide staining was not performed in the closed chest animals; therefore, cell death could not be demonstrated.

Premature vessel complexes also were noted in the open chest model at a mechanical index of 1.8 but not at a mechanical index of 1.0 or in the closed chest model (30). The increased vascular permeability produced by MCE is well recognized and is the basis for the use of MCE in gene and drug delivery. It is unclear how long this effect lasts or whether or not it is reversible. Of greater concern is the evidence of cell death noted in the open chest model at a mechanical index of 1.8. This study shows that, under proper experimental conditions, it is possible to produce mechanical tissue damage during MCE studies using commercially available agents and equipment. Although cautionary, the actual relevance of these finding to clinical practice remains unclear because, as the authors note, low mechanical index imaging at a low contrast does is unlikely to produce bioeffects, and current MCE protocols use low mechanical index imaging with only intermittent high mechanical index bursts.

CRT

The use of CRT has become an established treatment for patients with severe congestive heart failure and LV dyssynchrony. Echocardiography has proven important in determining the presence of dyssynchrony and evaluating the immediate and long-term effect of CRT on LV size and function. During the past year, new information has appeared on the optimal echocardiographic method from determining dyssynchrony, the predictive value of mechanical dyssynchrony in patients with QRS durations (≤120 ms), the long-term results of CRT, and the effects of CRT on the right ventricle

Predictive value of mechanical dyssynchrony in patients with normal QRS intervals. Until now, the selection of patients with heart failure for CRT therapy has been largely based on electrocardiographic criteria for prolonged activation (QRS >120 ms) based on the presumption that delayed activation would be required to produce delayed regional contraction. However, an increasing number of studies have reported dyssynchrony in a significant number of patients with QRS intervals <120 ms (31–33), and little is known about the prognostic significance of dyssynchrony in this group. To determine whether DTI measures of dyssynchrony were predictive of subsequent events (worsening congestive heart failure [CHF], cardiac transplantation, or death) Cho et al. (34) followed 106 patients (age 63 ± 11 years) with advanced CHF (EF <35%, New York Heart Association functional class II to IV) and a normal QRS interval (≤120 ms) for a mean of 17 ± 11 months. The presence of mechanical dyssynchrony was determined by DTI using an 8-segment model based on the standard deviation of time to peak systolic contraction ($Ts - SD$) and the maximal time difference between segments ($Ts - diff$). Patients with clinical events showed a greater mean age, increased prevalence of ischemic heart disease, longer QRS interval, lower use of beta-blockers, and significantly greater $Ts - SD$ and $Ts - diff$. There was a weak correlation between mechanical dyssynchrony and QRS duration (r = 0.26, p = 0.007). By multivariate analysis, $Ts - diff$ (>91 ms) was the only independent risk factor for clinical events and mortality in a model, including age, EF, QRS duration, and use of beta-blocking agents. Mean event-free survival was 16.3 in patients with *Ts − diff* (>91 ms) and 31.6 months in those with *Ts − diff* (≤91 ms) (34). These results, together with previous data from a smaller group of patients showing that CRT improves LV performance and clinical outcome in patients with heart failure and a QRS interval ≤120 ms, suggest that the use of electrocardiogram criteria alone may not be adequate for selecting patients for CRT and that this question deserves study in larger groups (35).

Radial vs. longitudinal strain. Suffoletto et al. (36) analyzed the potential of a speckle-tracking algorithm applied to midventricular short-axis images to determine dyssynchrony based on difference in time to peak radial strain. In 64 patients with CHF (EF ≤35%), a baseline septal to posterior wall delay of ≥130 ms predicted an immediate increase in stroke volume ≥15% in response to CRT with 91% sensitivity and 75% specificity and an improvement in EF (≥15%) in a subgroup (n = 50) followed for 8 ± 5 months with a sensitivity of 89% and a specificity of 83%. The increase in EF was greatest for patients with concordant lead placed with the site of latest activation. When compared with longitudinal DTI based on time to peak difference (>65 ms) or the 12 segment SD (>34 ms), overall sensitivity (89%) and specificity (75%) were similar. However, in 10% of patients with a favorable response to CRT radial dyssynchrony was not accompanied by longitudinal dyssynchrony and was attributed to the presence of prior apical infarction in 4 of 5. Although the authors present radial STE strain curves for multiple short axis segments, they present data for only the anterior and posterior segments and thus fail to examine the full potential of the technique or to demonstrate that it is superior to DTI measures of radial strain. Some of the difference in radial versus longitudinal strain may be explained by the previously reported differences in sensitivity of the 2 measures and suggest that it may be necessary to take fiber orientation into account when assessing dyssynchrony (2,32).

Long-term follow-up. To determine whether the reverse remodeling and symptomatic improvement noted at 6 months after CRT was sustained for 1 year, St. John Sutton et al. (37) performed serial Doppler echocardiograms in 228 patients enrolled in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial. The use of CRT resulted in progressive reverse remodeling that persisted to 12 months. After 12 months, LV volumes remained decreased versus the baseline (although slightly larger than at 6 months), LVEF in contrast progressively improved from 24.0 ± 6.1% at baseline to 29.2 ± 9.0% at 6 months, and 31.2 ± 11.4% at 12 months. Mitral regugitant jet area was significantly smaller than baseline but remained approximately constant from 6 to 12 months. Left ventricular mass showed progressive decline, and cavity shape returned toward normal. Importantly, the ongoing structural changes impacted favorably on symptoms (New York Heart Association functional class, quality of life score, and 6-min walk test). There changes were greater in nonischemic than in ischemic patients with heart failure (37).

Right ventricular (RV) remodeling. Although the beneficial effects of CRT on the LV have been extensively reported, little is known about the effects of this intervention on the RV. Accordingly, RV size, degree of tricuspid regurgitation, and pulmonary artery pressure were assessed in 56 patients with advanced heart failure (EF <35%) and left bundle branch block (QRS duration >120 ms) at baseline and 6 months after the initiation of CRT therapy. After 6 months of CRT, there was significant improvement in New York Heart Association functional class, 6-min walk, and quality of life score as well as an increase in LVEF, decrease in LVEDV and LVESV and mitral regurgitation grade. Pulmonary artery pressure also decreased (40 ± 12 mm Hg to 30 ± 11 mm Hg, $p < 0.001$), which was accompanied by a decrease in RV chamber size as measured in the apical 4-chamber view (long axis 89 ± 11 mm to 82 ± 10 mm, $p < 0.001$; midventricular short axis 29 ± 11 to 26 ± 7, $p < 0.001$; and tricuspid annular diameter 37 ± 9 to 32 ± 10, $p < 0.001$) and grade of tricuspid regurgitation (1.8 ± 0.8 to 1.3 ± 1.0, $p < 0.001$). Significant dyssynchrony (DTI septal to lateral wall delay >60 ms) was present in 44 patients (79%) and improvement in RV parameters was only noted in patients with significant LV dyssynchrony. The changes did not occur immediately after initiation of CRT and were most apparent in patients with the largest baseline RVs. Although the changes in RV size and degree of TR were presumably due to the decrease in pulmonary artery pressure, this relationship was not specifically examined (38).

Posterolateral scar. Because between 20% and 30% of heart failure patients fail to respond to CRT, it is important to understand the reasons for failure. Bleeker et al. (38) studied 40 consecutive patients chronic heart failure (EF <35%, QRS duration >120 ms) and coronary artery disease by DTI and MRI. Fourteen patients had a transmural scar (hyperenhancement extending from 51% to 100% of the LV wall thickness) in the posterolateral region (basal posterior, midposterior, posterolateral, and/or midposterolateral segments). Baseline characteristics between patients with (n = 14) and without (n = 26) posterolateral scar were comparable as was the QRS duration (158 ± 42 ms vs. 164 ± 26 ms, respectively; p = NS). Patients (n = 16) were classified as nonresponders to CRT based on clinical parameters (lack of improvement in New York Heart Association functional class, a lack of improvement >25% in the 6-min walking distance, or death before the 6 month follow-up). When the 4 different patient categories were compared (presence or absence of transmural scar in combination with presence or absence of severe baseline dyssynchrony ≥65 ms), only the patients with severe baseline dyssynchrony without scar (n = 22) showed an excellent response rate (95%) and the nonresponder had a nontransmural scar. Patients with severe LV dyssynchrony and the presence of a transmural posterolateral scar ($n = 11$) had a response rate of 18%, whereas those without baseline dyssynchrony had a poor response regardless of the presence ($n = 4$) or absence ($n = 3$) of posterolateral scar tissue. Thus, patients with CAD and posterolateral LV scar are unlikely to improve after CRT regardless of baseline LV dyssynchrony. Although the number of patients in this study was small, the results are intuitively attractive and deserve further study in larger groups (39).

PFO, Atrial Septal Aneurysm (ASA), and Stroke

To prospectively examine the relationship of PFO and ASA to stroke, Meissner et al. (40) studied an age- and gender-stratified random sample of the Olmsted County Minnesota population ($\geq$45 years of age, $n = 588$ or 47% of those eligible) who consented to multimodality testing, including record review, transesophageal echocardiography (TEE), and carotid ultrasonography. All individuals were followed for 5 years after entry into the study. Transesophageal echocardiography was successfully performed in 577 subjects and revealed a PFO in 140 (24.3%) and an ASA in 11 (1.9%). Of the 140 subjects with PFO, 6 (4.3%) had an ASA, whereas of the 437 subjects without a PFO, 5 had an ASA (1.1%, $p = 0.28$). During the median follow-up of 5.1 years, cerebrovascular events (including cerebrovascular disease-related death, ischemic stroke, and transient ischemic attack) occurred in 41 subjects. Of the 140 subjects with PFO, 12 had an ischemic event. No patient with PFO and a subsequent ischemic event had and ASA on TEE. After adjustment for age and comorbidity, PFO was not a significant independent predictor of stroke (hazard ratio 1.46, 95% confidence interval 0.74 to 2.88, $p = 0.28$). Two of the 5 patients with an isolated ASA had a cerebrovascular event, and the hazard ratio after adjusting for age and gender was nearly 4 times higher in patients with an ASA (3.72, 95% confidence interval 0.88 to 15.71) than in those without ASA. However, the absolute number of events was very small and did not reach statistical significance (40). The authors concluded from this prospective population data that, after correction for age and comorbidity, PFO was not an independent risk factor for future cerebrovascular events in the general population and noted that a larger study might be required to test the stroke risk associated with ASA.

This study is unique in that it prospectively follows a subgroup of a “randomly selected population,” only 6.3% of whom had a previous history of cerebrovascular disease before the index TEE. The prevalence of PFO in this study (24.3%) was similar to that expected in a random population. Although there was no difference in stroke in patients with and without PFO, the number of events in the PFO group was small ($n = 12$) and the patient group was older (mean age 66.9 years), where other causes of stroke would be expected to predominate. Lock estimated that <0.1% of individuals with a PFO will have an embolic stroke of “unknown” origin and, thus, it would take a much larger group to demonstrate this association (41). In addition, the study cannot address the difference in risk in younger patients (<55 years) where the relationship between PFO and stroke has been more convincingly demonstrated (42), since the number of younger patients was small and the number of events in this group although unstated, is presumably small as well. Thus, although there is clearly some association between the presence of a PFO and embolic stroke based on clinical and pathological evidence of paradoxical emboli and the repeated echocardiographic demonstration of examples of straddling thromboemboli that have become transiently trapped in the foramen ovale, the incidence in the general population is small and would require much larger studies to be clearly defined.

Low-gradient aortic stenosis (AS). Dobutamine stress echocardiography has been widely used to estimate operative risk in patients with low-gradient AS based on the presence or absence of contractile reserve (CR), which is defined as an increase in peak transaortic velocity >0.6 m/s, increase in stroke volume >20%, or increase in mean transvalvular pressure gradient >10 mm Hg). In a prospective French multicenter study of patients with low-gradient AS, Monin et al. (43) previously reported that operative mortality was 5% for patients with contractile reserve compared with 32% for those without contractile reserve. In a follow-up study from the same population, Quere et al. (44) identified 66 patients with symptomatic AS, a mean transvalvular gradient $\leq$40 mm Hg, and an LVEF $\leq$40% who survived valve replacement surgery and underwent a postoperative evaluation of functional status and LVEF (mean interval 16 $\pm$ 15 months). Before valve replacement surgery, 89% were in New York Heart Association functional class III or IV. Contractile reserve was present in 46 patients (70%). Compared with those with CR, those without had a similar postoperative functional status (class I or II: 93% vs. 85%, respectively), survival at 2 years (92% vs. 90%), increase in LVEF (19% vs. 17%), and postoperative EF (47% vs. 48%). Thus, although mortality as the result of surgery is clearly higher in patients without contractile reserve, if these patients survive surgery their outcome appears similar to those with contractile reserve.

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